Methods

Pharmacokinetic modelling of larotrectinib dose

The doses assigned to patients enrolled to cohorts 1 and 2 were based upon age and body surface area using nomograms designed to achieve AUC equivalent to adults treated at doses of 100 mg twice-daily (BID) and 150 mg BID, respectively, as predicted by SimCyp® modelling. Evaluating the pharmacokinetic data of patients enrolled to cohorts 1 and 2, it was apparent that the modelled doses resulted in lower AUC among young/small children than in older children and adults. Intrapatient dose escalation revealed generally dose-proportional increases in AUC. Following intrapatient dose escalation, the average larotrectinib dose in patients who achieved an AUC equal to that in adult patients was 100 mg/m^2/dose BID.

Based on the pharmacokinetics of larotrectinib in patients enrolled to cohorts 1 and 2, we calculated that a dose of 100 mg/m^2 BID, regardless of age, would achieve an AUC comparable to the adult RP2D. The protocol was amended to use this dose, with a cap of 100 mg/dose (the adult RP2D) for cohort 3. Following completion of enrolment to cohort 3, we analysed all patients treated on study with a dose of 80–125 mg/m^2 which totalled 19 patients (2 from cohort 1 and 8 from cohort 2 who were dose-escalated; and all 9 enrolled to cohort 3). Median $AUC_{0\text{-}24}$ of larotrectinib in cohort 3 was 3440, 4270, and 4790 ng*h/mL in patients aged <2, 2–11, and 12–18 years, respectively, which was comparable to the median AUC in adults treated at the RP2D, which was 4460 ng*h/mL (supplementary figure 1).

Results

Supplementary table 1: Participating centres

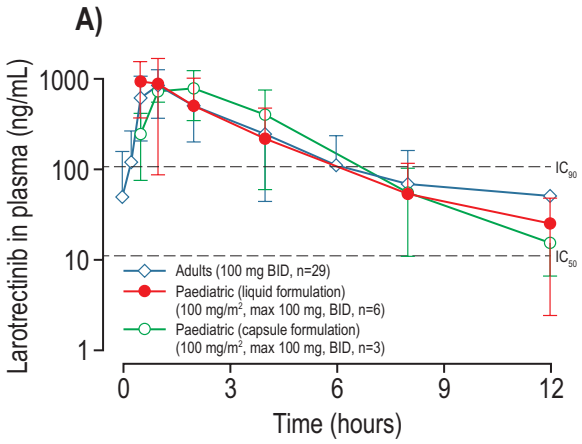
Centre	Principle investigator	Number of patients enrolled
University of Texas Southwestern Medical Center / Children's Health	Theodore W. Laetsch, MD	5
Seattle Children's Hospital, University of Washington, Fred Hutchinson Cancer Research Center	Catherine M. Albert, MD / Douglas S. Hawkins, MD	5
Children's Hospital Los Angeles, Keck School of Medicine, University of Southern California	Leo Mascarenhas, MD	4
Cincinnati Children's Hospital Medical Center	Brian Turpin, DO	2
Dana-Farber/Boston Children's Cancer and Blood Disorders Center and Harvard Medical School	Steven G. DuBois, MD	2
Nemours Children's Hospital	Ramamoorthy Nagasubramanian, MD	2
St Jude Children's Research Hospital	Alberto S. Pappo, MD	2
University of California, Los Angeles	Noah Federman, MD	2

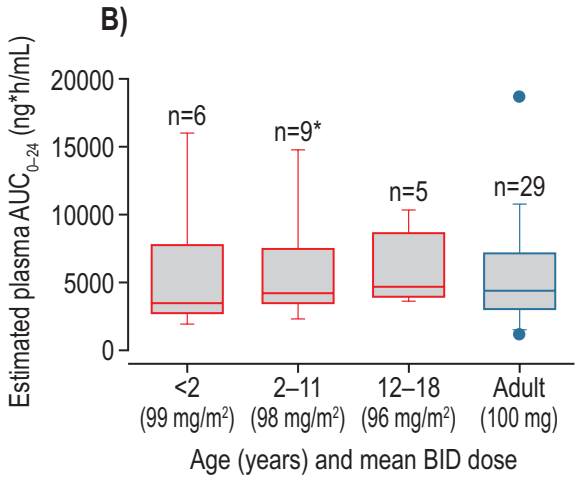
Supplementary table 2: All larotrectinib-related treatment-emergent adverse events

	Overall (n=24)					100 mg/m2 BID (n=9)				
Preferred Term	**All Grades**	**Grades 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**All Grades**	**Grades 1-2**	**Grade 3**	**Grade 4**	**Grade 5**
At Least One Related TEAE	22 (92%)	21 (88%)	4 (17%)	0	0	8 (89%)	8 (89%)	2 (22%)	0	0
Alanine aminotransferase increased	10 (42%)	9 (38%)	1 (4%)	0	0	3 (33%)	2 (22%)	1 (11%)	0	0
Aspartate aminotransferase increased	10 (42%)	10 (42%)	0	0	0	4 (44%)	4 (44%)	0	0	0
Leukocyte count decreased	5 (21%)	5 (21%)	0	0	0	2 (22%)	2 (22%)	0	0	0
Neutrophil count decreased	5 (21%)	4 (17%)	1 (4%)	0	0	3 (33%)	2 (22%)	1 (11%)	0	0
Vomiting	5 (21%)	5 (21%)	0	0	0	2 (22%)	2 (22%)	0	0	0
Anaemia	4 (17%)	4 (17%)	0	0	0	2 (22%)	2 (22%)	0	0	0
Constipation	4 (17%)	4 (17%)	0	0	0	2 (22%)	2 (22%)	0	0	0
Hypoalbuminaemia	4 (17%)	4 (17%)	0	0	0	1 (11%)	1 (11%)	0	0	0
Nausea	4 (17%)	3 (13%)	1 (4%)	0	0	3 (33%)	2 (22%)	1 (11%)	0	0
Blood creatinine increased	3 (13%)	3 (13%)	0	0	0	1 (11%)	1 (11%)	0	0	0
Fatigue	3 (13%)	3 (13%)	0	0	0	1 (11%)	1 (11%)	0	0	0
Blood alkaline phosphatase increased	2 (8%)	2 (8%)	0	0	0	1 (11%)	1 (11%)	0	0	0
Hyperkalaemia	2 (8%)	2 (8%)	0	0	0	1 (11%)	1 (11%)	0	0	0
Insomnia	2 (8%)	2 (8%)	0	0	0	0	0	0	0	0
Protein total decreased	2 (8%)	2 (8%)	0	0	0	2 (22%)	2 (22%)	0	0	0
Abdominal pain	1 (4%)	1 (4%)	0	0	0	1 (11%)	1 (11%)	0	0	0
Alopecia	1 (4%)	1 (4%)	0	0	0	1 (11%)	1 (11%)	0	0	0
Anorexia and bulimia syndrome	1 (4%)	1 (4%)	0	0	0	0	0	0	0	0
Anxiety	1 (4%)	1 (4%)	0	0	0	0	0	0	0	0
Blood cholesterol increased	1 (4%)	1 (4%)	0	0	0	0	0	0	0	0
Delirium	1 (4%)	1 (4%)	0	0	0	0	0	0	0	0
Diarrhoea	1 (4%)	1 (4%)	0	0	0	0	0	0	0	0
Dizziness	1 (4%)	1 (4%)	0	0	0	1 (11%)	1 (11%)	0	0	0
Dry skin	1 (4%)	1 (4%)	0	0	0	1 (11%)	1 (11%)	0	0	0
Ejection fraction decreased	1 (4%)	0	1 (4%)	0	0	0	0	0	0	0
Flatulence	1 (4%)	1 (4%)	0	0	0	1 (11%)	1 (11%)	0	0	0
Haematuria	1 (4%)	1 (4%)	0	0	0	0	0	0	0	0
Hypernatraemia	1 (4%)	1 (4%)	0	0	0	0	0	0	0	0
Hypertension	1 (4%)	1 (4%)	0	0	0	0	0	0	0	0

Increased appetite	1 (4%)	1 (4%)	0	0	0	0	0	0	0	0
Lymphocyte count decreased	1 (4%)	1 (4%)	0	0	0	0	0	0	0	0
Pain in extremity	1 (4%)	1 (4%)	0	0	0	1 (11%)	1 (11%)	0	0	0
Pharyngeal inflammation	1 (4%)	1 (4%)	0	0	0	0	0	0	0	0
Platelet count decreased	1 (4%)	1 (4%)	0	0	0	1 (11%)	1 (11%)	0	0	0
Sinus tachycardia	1 (4%)	1 (4%)	0	0	0	1 (11%)	1 (11%)	0	0	0
Skin sensitisation	1 (4%)	1 (4%)	0	0	0	1 (11%)	1 (11%)	0	0	0
Weight increased	1 (4%)	0	1 (4%)	0	0	0	0	0	0	0

Supplementary figure 1: A. Capsule and liquid pharmacokinetics for larotrectinib in children. B. Larotrectinib area under the curve.





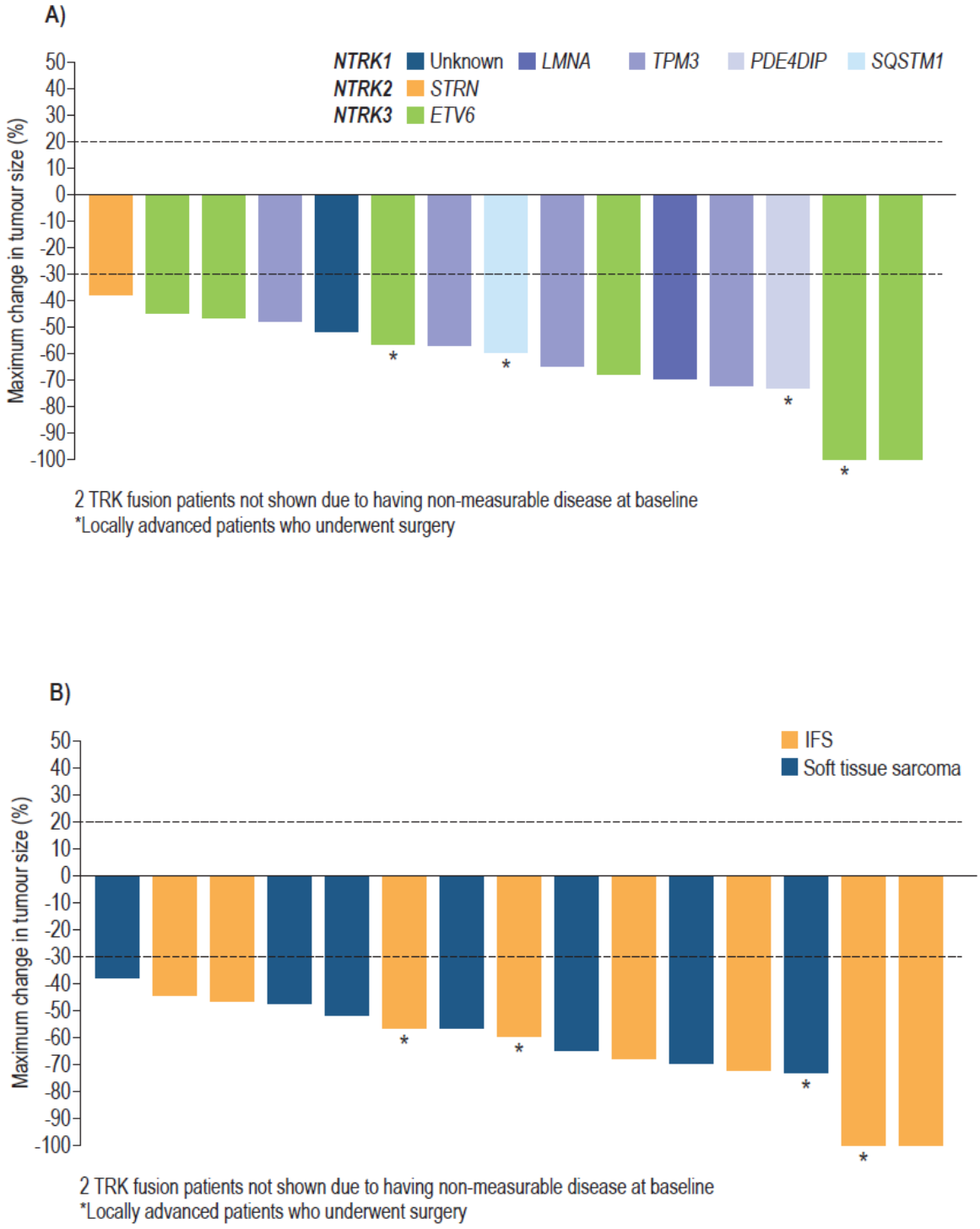
Population	N	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24} (ng*h/mL)	$T_{1/2}$ (h)
Paeds liquid	6	1010 ± 740	0·75 (0·5–1)	5570 ± 5400	1·9 ± 0·3
Paeds capsule	3	882 ± 295	2 (1–2)	6689 ± 3860	1·5 ± 0·2
Adult capsule	29	908 ± 419	1	5340 ± 3520	2·0 ± 0·7

C_{max}, AUC_{0-24}, and $T_{1/2}$ are mean ± standard deviation; T_{max} is median (range)

Age Range (years)	N	AUC_{0-24} (ng*h/mL) Mean ± SD
<2	6	5463 ± 5270
2–11	9*	5808 ± 3844
12–18	5	5970 ± 2791
Adult	29	5340 ± 3520

*One patient included in both <2 and 2–11 year categories (due to aging while on study)

Supplementary figure 2: Waterfall plot of maximal change in tumour size in TRK fusion patients by independent radiology read. Bars are colour coded by *NTRK* fusion and partner (A) and histological diagnosis (B).



Supplementary figure 3: Kaplan-Meier plot of duration of response for patients with investigator assessed confirmed objective response